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Title of Invention: Enteric preparation of mexiletine hydrochloride

Abstract:

Purpose of Invention: To provide an enteric preparation of mexiletine hydrochloride with few side effects on the digestive organs.

Constitution of Invention: A solid preparation of mexiletine hydrochloride, the surface of which is coated with an enteric coating material.

Claims:

(1) A solid preparation containing mexiletine hydrochloride, the surface of which is coated with an enteric coating material.

(2) A solid preparation in accordance with Claim 1, in which said solid preparation is selected from tablets, powders, granules, and capsules.

(3) A solid preparation in accordance with Claim 1, in which said enteric coating material is selected from hydroxypropyl methyl cellulose phthalate 220824, hydroxypropyl methyl cellulose phthalate 200731, hydroxypropyl methyl cellulose acetate succinate, carboxymethyl ethyl cellulose, methacrylate copolymer L, methacrylate copolymer LD, and cellulose acetate phthalate.

Detailed Explanation of Invention:

[0001]

Field of Use in Industry

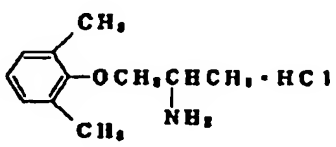
This invention concerns an enteric preparation of mexiletine hydrochloride with few side effects on the digestive organs.

[0002]

Prior Art

Mexiletine hydrochloride is a medicinal substance which is useful as a drug for treating arrhythmia; its chemical formula is

[0003]



[0004] This substance has the electrophysiological activity of reducing the maximum depolarization rate and shortening the active potential duration time. It also reduces the slope of the slow diastolic depolarization phase and suppresses automaticity. This substance is also recognized as one which suppresses various kinds of experimental arrythmia, such as coronary artery two-step ligatures, and it is clinically effective against tachyarrhythmia (ventricular). It has few effects on the sinus cycle, the stimulus transmission system, and thee electrocardiogram wave pattern, and has comparatively few effects on the kinetics of circulation; therefore, it is widely used in treating arrhythmias. Since it has a high rate of appearance of the side effect of kidney disorders, however, this has been a great obstacle to its use in therapy by oral administration.

[0005] At present, the only formulations of mexiletine hydrochloride on the market have been capsules which are filled with it as is and an injectable solution. Since it has a strong irritating effect on mucous membranes, there is a concern for the oral capsule, in particular, that if it sticks to the esophagus and stays there until it disintegrates, the mexiletine hydrochloride will directly contact the mucous membrane and thus cause an esophageal ulcer. Furthermore, side effects on the digestive organs have been seen with a high frequency, including nausea, and occasionally anorexia, heartburn, upset stomach, upper abdominal pain, vomiting, abdominal bloating, etc. According to side effects reports of the Ministry of Health, side effects are seen in 14.04% of the patients to whom it is administered, and considering the cases which go unreported in addition, one may suppose that the frequency of appearance is even higher than this. Because of these side effects, oral administration is a problem demanding solution. Furthermore, injectable preparations, which have fewer side effects on the digestive organs (rate of appearance of side effects: 3.98%), have also been proposed, but they also cause great distress to patients, except in emergency use, and have not been a desirable form for long-term treatment.

[0006] The inventors investigated various formulations of orally administered mexiteline hydrochloride for reducing the rate of appearance of side effects, such as compounds with antacid agents, agents for protecting the stomach mucosa, etc. However, none of them showed an effect of reducing side effects. Therefore, they performed various studies, as a result of which they succeeded in providing the novel formulation of this invention, which prevents the appearance of side effects without impeding the absorption of the effective substance by coating the surface of the formulation by using an enteric coating that does not break down in the stomach.

[0007]

Description of the Invention

This invention provides a solid formulation, which is characterized by the fact that the surface of a solid formulation containing mexiletine hydrochloride is coated with an enteric coating material.

[0008] This invention will be explained in detail below. The solid formulation in this invention may be a tablet, granule, or capsule as provided for in the Japan Pharmacopoeia, as well as any form of the drug which can be made into a solid formulation which can be coated with an enteric coating materials, such as a granulated powdered drug (Pharmacopoeia 9), fine granules (Pharmacopoeia 10), etc., which are presently included in the category of "powdered drugs" (Pharmacopoeia 12).

[0009] Examples of the enteric coating material mentioned above include hydroxypropyl methyl cellulose phthalate 220824, hydroxypropyl methyl cellulose phthalate 200731, and cellulose acetate phthalate, which are listed in the Japan Pharmacopoeia, as well as hydroxypropyl methyl cellulose acetate succinate, carboxymethyl ethyl cellulose, methacrylate copolymer L, and methacrylate copolymer LD, which are listed in the 1991 edition of the Japan Pharmacopoeia External Pharmaceutical Ingredients (edited by the Ministry of Health). They may be used individually or in mixtures. Since the mexiletine hydrochloride formulation obtained by this invention has the same absorbability of the effective substance as the conventional capsule formulation, it does not impair the therapeutic efficacy of the drug itself, and in addition, since it does not break down in the stomach, stomach lesions are prevented or alleviated. Therefore, treatment by oral administration of mexiletine hydrochloride in actual therapeutic situations is facilitated and a suitable therapeutic effectiveness is obtained.

[0010] This invention will be explained in further detail below by working examples, comparison examples, and experimental examples.

[0011] Working Example 1

Tablets were prepared according to the following formulation:

Per tablet:	
Mexiletine hydrochloride	50.0 mg
Milk sugar	4.0 mg
Hydroxypropyl cellulose	0.5 mg
Magnesium stearate	0.5 mg
Hydroxypropyl methyl cellulose phthalate 200731	8.1 mg
Titanium oxide	0.09 mg
Glycerol fatty acid ester	0.81 mg
Total	64.0 mg

[0012] Method of preparation

1) Forty grams milk sugar were added to 500 g mexiletine hydrochloride; after they were mixed, a binder made by dissolving 5 g hydroxypropyl cellulose in 120 g Pharmacopoeia ethanol was added and granules were formed with a vertical granulator

(Powrex Co.). After these granules were dried, 5 g magnesium stearate were added; after mixing, 10,000 raw tablets were produced with a rotary tablet stamping machine (Hata Iron Works Co., HT-P22); each tablet weighed 55 mg and had a diameter of 5.5 mm.

[0013] 2) A coating material consisting of 1500 g Pharmacopoeia ethanol, 1410 g dichloromethane, 81 g hydroxypropyl methyl cellulose phthalate 200731 (Shin-etsu Chemical Co.), 8.1 g glycerol fatty acid ester, and 0.9 g titanium oxide was applied to the raw tablets obtained in 1) to form a film coating (9 mg per tablet), using a High Coater (Freund Industrial Co.) In this manner, enteric-film-coated tablets were prepared.

[0014] Working Example 2

Tablets were prepared according to the following formulation:

Per tablet:	
Mexiletine hydrochloride	50.0 mg
Milk sugar	4.0 mg
Hydroxypropyl cellulose	0.5 mg
Magnesium stearate	0.5 mg
Methacrylate copolymer-L	6.86 mg
Titanium oxide	0.09 mg
Glycerol fatty acid ester	0.81 mg
Total	64.0 mg

[0015] Method of preparation

1) Forty grams milk sugar were added to 500 g mexiletine hydrochloride; after they were mixed, a binder made by dissolving 5 g hydroxypropyl cellulose in 120 g Pharmacopoeia ethanol was added and granules were formed with a vertical granulator (Powrex Co.). After these granules were dried, 5 g magnesium stearate were added; after mixing, 10,000 raw tablets were produced with a rotary tablet stamping machine (Hata Iron Works Co., HT-P22); each tablet weighed 55 mg and had a diameter of 5.5 mm.

[0016] 2) A coating material consisting of 1500 g Pharmacopoeia ethanol, 1410 g dichloromethane, 68.1 g methacrylate copolymer-L (Roehm Pharma Co., Eudragit L), 21 g talc, and 0.9 g titanium oxide was applied to the raw tablets obtained in 1) to form a film coating (9 mg per tablet), using a High Coater (Freund Industrial Co.). In this manner, enteric-film-coated tablets were prepared.

[0017] Working Example 3

Granules were prepared according to the following formulation:

Per granule:	
Mexiletine hydrochloride	100 mg
Milk sugar	665 mg
Hydroxypropyl cellulose	35 mg
Methacrylate copolymer-L	152 mg
Titanium oxide	2 mg
Talc	46 mg
Total	1000 mg

[0015] Method of preparation

1) 3325 g milk sugar were added to 500 g mexiletine hydrochloride; after they were mixed, a binder made by dissolving 175 g hydroxypropyl cellulose in 1575 g Pharmacopoeia ethanol was added and granules were formed with a vertical granulator (Powrex Co.), at the size of 18 mesh, and dried.

[0019] 2) A coating material consisting of 6000 g Pharmacopoeia ethanol, 6000 g dichloromethane, 760 g methacrylate copolymer-L (Roehm Pharma Co., Eudragit L), 21 g talc, and 0.9 g titanium oxide was applied to the granules obtained in 1) to form a 20% film coating, using a Flow Coater (Freund Industrial Co.). In this manner, enteric granules were prepared.

[0020] Working Example 4

1) Capsules were prepared according to the following formulation:

Per capsule:	
Mexiletine hydrochloride	50.0 mg
Milk sugar	7.0 mg
Hydroxypropyl cellulose	3.0 mg
Methacrylate copolymer-L	13.7 mg
Titanium oxide	0.2 mg
Talc	4.1 mg
Total	78.0 mg

[0021] Method of preparation

1) One hundred forty grams milk sugar were added to 1000 g mexiletine hydrochloride; after they were mixed, a binder made by dissolving 60 g hydroxypropyl cellulose in 540 g Pharmacopoeia ethanol was added and granules were formed with a vertical granulator (Powrex Co.), at the size of 18 mesh, and dried.

[0022] 2) A coating material consisting of 282g Pharmacopoeia ethanol, 282 g dichloromethane, 27.3 g methacrylate copolymer-L (Roehm Pharma Co., Eudragit L), 8.3 g talc, and 0.4 g titanium oxide was applied to the granules obtained in 1) to form a 30% film coating, using a Flow Coater (Freund Industrial Co.). In this manner, enteric granules were prepared.

[0023] 3) Capsules were prepared by filling Japan Pharmacopoeia hard capsules (No. 4 capsules) with 78 mg per capsule of the enteric granules obtained in 2).

[0024] Working Example 5

1) Capsules were prepared according to the following formulation:

Per capsule:	
Mexiletine hydrochloride	50.0 mg
Milk sugar	6.5 mg
Hydroxypropyl cellulose	3.0 mg
Magnesium stearate	0.5 mg
Total	60.0 mg

[0025] Formulation of enteric coating agent, per capsule

Methacrylate copolymer-L	15.2 mg
Titanium oxide	0.2 mg
Talc	4.6 mg
Total	20.0 mg

[0026] Method of preparation

1) One hundred thirty grams milk sugar were added to 1000 g mexiletine hydrochloride; after they were mixed, a binder made by dissolving 60 g hydroxypropyl cellulose in 540 g Pharmacopoeia ethanol was added and granules were formed with a vertical granulator (Powrex Co.), at the size of 18 mesh, and dried.

[0027] 2) Ten grams magnesium stearate were added to the granules obtained in 1) and mixed with them.

[0028] 3) Japan Pharmacopoeia hard capsules (No. 5 capsules) were filled with 60 mg per capsule of the mixture obtained in 2) to prepare capsules.

[0029] 4) A coating material consisting of 2300 g Pharmacopoeia anhydrous ethanol, 2300 g dichloromethane, 304 g methacrylate copolymer-L (Roehm Pharma Co., Eudragit L), 92 g talc, and 4 g titanium oxide was applied to the capsules obtained in 4) to form a film coating (20 mg per capsule), using a High Coater (Freund Industrial Co.). In this manner, enteric capsules were prepared.

[0030] Working Example 6

Fine granules were prepared according to the following formulation:

Per gram:	
Mexiletine hydrochloride	100 mg
Milk sugar	665 mg
Hydroxypropyl cellulose	35 mg
Methacrylate copolymer-L	152 mg
Titanium oxide	2 mg
Talc	46 mg
Total	1000 mg

[0031] Method of preparation

1) 3325 g milk sugar were added to 500 g mexiletine hydrochloride; after they were mixed, a binder made by dissolving 175 g hydroxypropyl cellulose in 1575 g Pharmacopoeia ethanol was added and granules were formed with a vertical granulator (Powrex Co.), at the size of 42 mesh, and dried.

[0032] 2) A coating agent consisting of 6000 g Pharmacopoeia ethanol, 6000 g dichloromethane, 760 g methacrylate copolymer-L (Roehm Pharma Co., Eudragit L), 21 g talc, and 0.9 g titanium oxide was applied to the fine granules obtained in 1) to form a film coating (20% with respect to the granules). In this manner, enteric fine granules were prepared.

[0033] Comparison Example 1

Capsules were prepared according to the following formulation, based on a commercial product:

Per capsule:	
Mexiletine hydrochloride	50.0 mg
Corn starch	25.0 mg
Light anhydrous silicic acid	2.0 mg

Magnesium stearate	3.0 mg
Total	80.0 mg

[0034] Method of preparation

Two hundred fifty grams corn starch, 20 g light anhydrous silicic acid, and 30 g magnesium stearate were added to 500 g mexiletine hydrochloride; after they were mixed, Japan Pharmacopoeia hard capsules (No. 4 capsules) were filled with 80 mg per capsule of the mixture to prepare capsules.

[0035] Experimental Example 1

The dissolution rates of the enteric tablets obtained in Working Example 1 and the slow-release capsules prepared in Comparison Example 1 were compared by performing the Japan Pharmacopoeia Dissolution Test Method 2 (paddle method), using 900 ml of break-down test solution 1 (pH 1.2) and the same quantity of solution 2 (pH 6.8).

[0036] Measurement results

Fig. 1 shows dissolution change curve of the enteric tablets of Working Example 1 and the capsules of Comparison Example 1 with solution 1 (pH 1.2), and Fig. 2 shows dissolution change curves with solution 2 (pH 6.8). Comparing them, the capsules of the comparative example were observed to dissolve rapidly in solutions 1 and 2, whereas it was observed that the enteric tablets of Working Example 1 did not dissolve in solution 1and rapidly dissolved in solution 2.

[0037] Experimental Example 2

The blood concentrations for the enteric tablets of Working Example 1 and the capsules of Comparison Example 1 were compared.

[0038] Six male beagles, weighing approximately 10 kg, were divided into 2 groups. They were fasted overnight before the drugs were administered. A quantity of preparation corresponding to 100 mg mexiletine hydrochloride (2 50 mg tablets) was administered orally. After the administration, the dogs were made to drink 30 ml water. Approximately 3 ml blood were drawn from a forelimb vein before the administration and 1, 2, 3, 4, 5, 6, 8, 10, and 24 hours after it. The samples were centrifuges to obtain the plasma. One milliliter 0.1N NaOH and n-hexane were added to 1 ml of this plasma to perform extraction; the extracted solution was distilled off under a vacuum, after which the residue was dissolved in 200 μl internal standard solution (1 μg/ml ethyl p-oxybenzoate) to make a sample solution. The mexiletine hydrochloride concentrations in each plasma were measured by using high-performance liquid chromatography, under the following conditions: mobile phase, 0.025 M phosphate buffer (pH 3.0) : acetonitrile solution (7:3); measurement wavelength 210 nm; flow rate 1 ml/min.

[0039] Measurement results

Figs. 3 and 4 show the plasma concentration curves of the enteric tablets of Working Example 1 and those of Comparison Example 1, respectively. Comparing them, it was observed that the area under the blood concentration curve (AUC) for the tablets Working Example 1 was 12.825 $\mu g \cdot hr/ml$, and that for those of Comparison Example 1 was 12.476 $\mu g \cdot hr/ml$. Thus, no significant difference was seen. The peak blood concentration (C_{max}) was 1.101 $\mu g/ml$ for Working Example 1 and 1.434 $\mu g/ml$ for Comparison Example 1. The tablets of working Example 1 showed no rapid rise in blood concentration, and their C_{max} was decreased by approximately 30%.

[0040] Experimental Example 3

Six male beagles, weighing 9.4–10.4 kg, were divided into 2 groups of 3 each. Each dog was orally administered 2 enteric tablets prepared in Working Example 1 (100 mg as mexiteline hydrochloride) and 2 capsules of Comparison Example 1 (100 mg as mexilitine hydrochloride) once a day for 14 days, and their conditions were observed. As a result, it was observed, as shown in Table 1, that a vomiting phenomenon was observed in the dogs which received the capsules of Comparison Example 1, after day 7, and a slight decrease in their body weight was seen, but the dogs to which the tablets prepared in Working Example 1 were given did not show a vomiting phenomenon, and the side effect symptoms in the digestive organs were considerably ameliorated. The results are shown in Table 1.

[0041]

Table 1

Beagles		Before administration	After 1 week	After 2 weeks
Comparison Example 1	No. 1	9.4 kg No vomiting	9.4 kg No vomiting	9.0 kg Vomiting
	No. 2	10.1 kg No vomiting	9.4 kg Vomiting	9.5 kg Vomiting
	No. 3	10.4 kg No vomiting	10.1 kg No vomiting	10.1 kg No vomiting
Working Example 1	No. 4	10.2 kg No vomiting	10.1 kg No vomiting	10.3 kg No vomiting
	No. 5	9.6 kg No vomiting	10.1 kg No vomiting	10.3 kg No vomiting
	No. 6	9.4 kg No vomiting	9.9 kg No vomiting	10.5 kg No vomiting

[0042]

Effectiveness of Invention

From the results of these experiments, the following facts were observed:

1) With the formulation of this invention, the plasma concentration is easily controlled. With the mexiletine hydrochloride presently on the market, especially oral capsules, the effective therapy range is comparatively narrow and the rate of appearance of side effects is high; therefore, there was the problem that suitable therapies for arrhythmia patients could not be performed in actual clinical situations, because of the side effects of the mexiletine hydrochloride.

[0043] 2) With the formulation of this invention, side effects such as esophageal ulcers and stomach lesions can be reduced.

[0044] 3) With the formulation of this invention, excess elevation of the blood level, which is thought to cause central nervous system side effects, is suppressed; therefore, suitable therapies, with few side effects, can be devised.

Simple Explanation of Drawings:

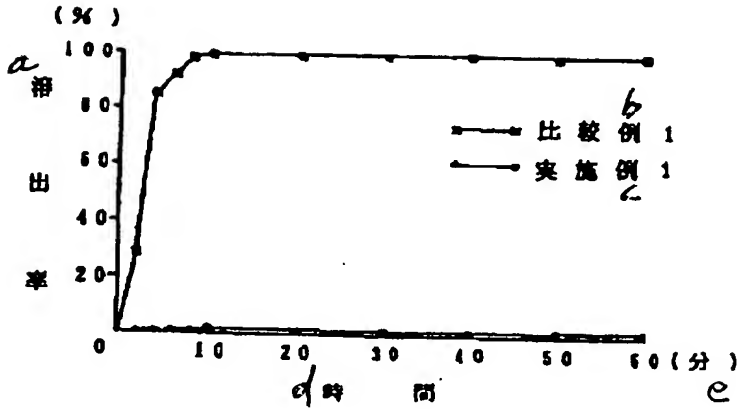
Fig. 1: A graph showing dissolution change curves of capsules of the enteric tablets obtained in Working Example 1 and Comparison Example 1

Fig. 2: A graph showing dissolution change curves of capsules of the enteric tablets obtained in Working Example 1 and Comparison Example 1

Fig. 3: A graph showing a plasma concentration curve of the enteric tablets obtained in Working Example 1

Fig. 4: A graph showing a plasma concentration curve of the capsules of Comparison Example 1

Fig. 1



a. Dissolution rate

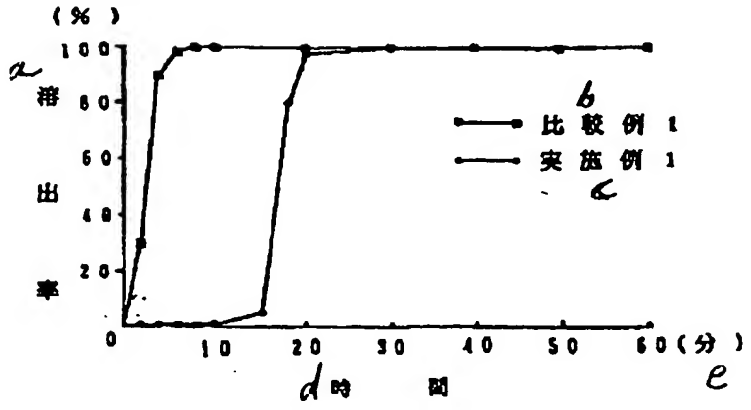
b. Comparison Example 1

c. Working Example 1

d. Time

e. (Minutes)

Fig. 2



a. Dissolution rate

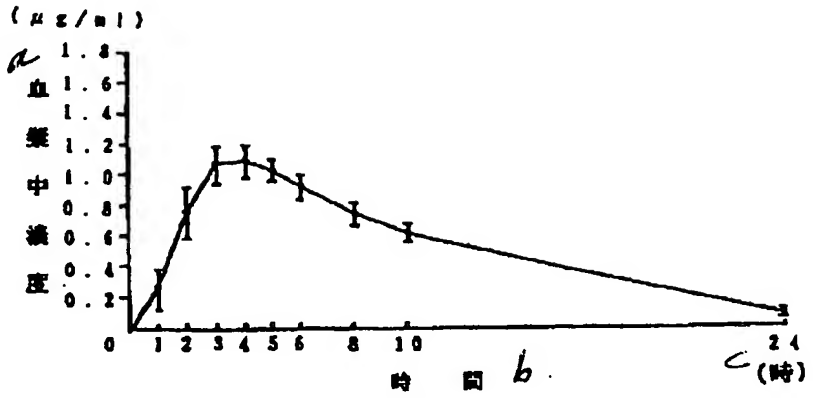
b. Comparison Example 1

c. Working Example 1

d. Time

e. (Minutes)

Fig. 3

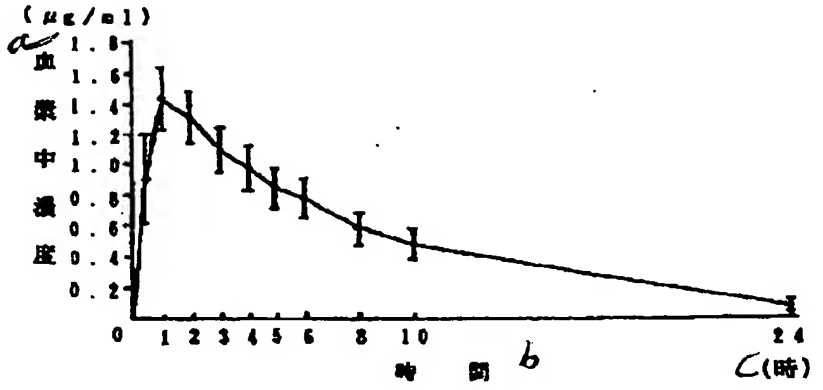


a. Plasma concentration

b. Time

c. (Hours)

Fig. 4



a. Plasma concentration

b. Time

c. (Hours)